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From Sugar to Fat:

How the Transcription Factor XBP1 Regulates Hepatic Lipogenesis

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Abstract

Lipogenesis occurs primarily in the liver, where dietary carbohydrates control the expression of key enzymes in glycolytic and lipogenic pathways. We have recently discovered that the transcription factor XBP1, best known as a key regulator of the unfolded protein response (UPR), is required for *de novo* fatty acid synthesis in the liver, a function unrelated to its role in the UPR.¹ XBP1 protein expression is induced in the liver by a high carbohydrate diet and directly controls the induction of critical genes involved in fatty acid synthesis. Specific deletion of XBP1 in adult liver using an inducible approach results in profound hypocholesterolemia and hypotriglyceridemia, which could be attributed to diminished production of lipids in the liver. Notably, this phenotype is not associated with fatty liver (hepatic steatosis) or significant compromise in protein secretion. XBP1 joins an already rich field of transcriptional regulatory proteins in the control of hepatic lipogenesis. Its function in lipogenesis appears to be highly significant as evidenced by the phenotype of the genetic mutant strain. A more complete understanding of the mechanisms by which XBP1 accelerates *de novo* fatty acid synthesis in the liver while preserving normal hepatic lipid composition is highly relevant to the treatment of diseases such as atherosclerosis and metabolic syndrome that are associated with dyslipidemia. Since excess fat accumulation in the liver could result from increased hepatic fatty acid synthesis, compounds that inhibit XBP1 activation may also be useful therapeutics for the treatment of human alcoholic liver disease (ALD) and nonalcoholic fatty liver disease (NAFLD), increasingly common causes of morbidity and mortality in the United States.

Keywords

XBP1; liver; lipogenesis; dyslipidemia; transcription; triglycerides; cholesterol

Introduction

The incidence of metabolic syndrome, a condition characterized by the constellation of central obesity, dyslipidemia, hepatic steatosis, elevated blood glucose, and hypertension, continues to rise in industrialized nations.² Dyslipidemia, manifested by elevated levels of plasma triglyceride (TG) and low density lipoprotein (LDL) cholesterol and low levels of high density lipoprotein (HDL) cholesterol, is a risk factor for coronary artery disease.³

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Conflicts of Interest

The authors declare no conflicts of interest.

Increased *de novo* synthesis and secretion of lipids from the liver contributes significantly to the hepatic steatosis and dyslipidemia associated with type 2 diabetes.^{1, 2, 4} In healthy individuals, hepatic lipogenesis is activated after ingestion of high-carbohydrate, low-fat diet to generate fat from dietary carbohydrate. Insulin plays a critical role in this process by activating a well-characterized lipogenic transcription factor, SREBP-1c.^{5, 6} In the insulin-resistant state, elevated circulating insulin further stimulates fatty acid synthesis and very low density lipoprotein (VLDL) secretion, as observed in genetically modified obese (ob/ob) mice, aggravating insulin resistance.⁷ Control of dyslipidemia in patients with coronary artery disease with the statins, agents that target 3-methylglutaryl-coenzyme A (HMG CoA) reductase, and with triglyceride-lowering agents has resulted in measurable improvements in cardiovascular morbidity and mortality, suggesting clinical benefits of lowering hepatic *de novo* lipid synthesis.⁸

The Transcription Factor XBP1

The transcription factor XBP1 has been identified as a key regulator of the mammalian unfolded protein response (UPR) or endoplasmic reticulum (ER) stress response, which is activated by environmental stressors such as protein overload that require increased ER capacity.⁹ XBP1 is activated by a post-transcriptional modification of its mRNA by inositol requiring enzyme 1 (IRE1), an ER-localizing proximal sensor of ER stress that is a Ser/Thr protein kinase and endoribonuclease.^{10–13} Upon ER stress, IRE1 induces an unconventional splicing of XBP1 mRNA by using its endoribonuclease activity to generate a mature mRNA encoding an active transcription factor,^{10–14} XBP1s, which directly binds to the promoter region of its target genes to promote transcription.^{15–17} In mammalian cells, a 26-nucleotide intron of XBP1 mRNA is spliced out by activated IRE1, leading to a shift in the codon reading frame. Translation of the new reading frame results in the conversion of XBP1 from an unspliced form of 261 amino acids (in human) to a spliced form of 376 amino acids that comprises the original N-terminal DNA binding domain plus an additional, potent transactivation domain in the C terminus.^{10–12, 14} XBP1 mRNA is the only known substrate of the ribonuclease activity of IRE1 in metazoans, as is the case in yeast, in which a genome-wide search failed to identify any additional substrates.¹⁸ While the function of XBP1 in hepatic lipogenesis is unrelated to its function in the UPR (see below), it nevertheless requires splicing by IRE1 α . Although IRE1 is the most evolutionarily conserved branch of the UPR, little is known about the regulation of its activity or about its function *in vivo*. IRE1 $\alpha^{-/-}$ mice have defects in embryonic liver development but die earlier in embryogenesis than XBP1 $^{-/-}$ embryos.¹⁹ In insect cells, active IRE1 was recently proposed to control the degradation of mRNAs encoding certain ER proteins that were predicted to be difficult to fold.²⁰ The function of XBP1u protein translated from the unspliced XBP1 mRNA is largely unknown, but it may heterodimerize with XBP1s protein to suppress XBP1s function under certain circumstances.^{21, 22} XBP1s protein controls the up-regulation of a broad spectrum of UPR-related genes involved in protein folding, redox metabolism, ER-associated degradation and protein quality control.^{15–17, 23} Mice deficient in XBP1 display severe abnormalities in the development and function of professional secretory cells, such as plasma B cells and pancreatic acinar cells.^{24, 25} Secretion of immunoglobulin and zymogens from these cells is dramatically decreased in XBP1 $^{-/-}$ mice, due to ER stress-induced apoptosis during development. XBP1 is also required for embryonic liver development, although its function in the adult liver is unknown.²⁶ To establish the function of XBP1 in the adult liver, we generated Xbp1 Δ mice with an inducible, conditional disruption of the Xbp1 gene in the liver. Unexpectedly, our analysis revealed an essential role for XBP1 in hepatic lipid synthesis that was unrelated to its function in the ER stress response.

Control of Hepatic Lipogenesis

In mammals, the liver is the principal organ that controls energy homeostasis through regulating carbohydrate metabolism and fatty acid synthesis. During starvation, the liver produces glucose to maintain circulating glucose levels by breaking down glycogen stores or by synthesizing glucose through gluconeogenesis. In contrast, ingestion of dietary carbohydrates promotes lipid synthesis in the liver to convert carbohydrates to TG for long-term energy storage.²⁷ TG is packaged in very low-density lipoprotein (VLDL) particles and then transported to the adipose tissue.²⁸ Hepatic lipid metabolism is coordinated by multiple factors such as pancreatic hormones and circulating glucose levels under different nutritional conditions. Transcription factors sterol regulatory element binding protein (SREBPs) and carbohydrate-response element-binding protein (ChREBP) play essential roles in controlling the genetic program for lipid synthesis in the liver (Fig. 1).^{5, 6, 29} It has been demonstrated that SREBP-1c and SREBP-2 primarily regulate genes involved in fatty acid and cholesterol synthesis pathways, respectively,^{5, 6} while ChREBP regulates genes involved in glycolysis and fatty acid synthesis.²⁹ Upon carbohydrate intake, insulin produced from the pancreas transcriptionally activates SREBP-1c,³⁰ while glucose promotes ChREBP dephosphorylation and its subsequent nuclear translocation.³¹ SREBP-1c and ChREBP are also transcriptionally activated by the nuclear receptor liver $\times$ receptor (LXR), which appears to serve as a glucose sensor.³²

SREBP-1c is a member of the bZIP transcription factor family.^{6, 33} SREBPs are produced as precursor forms that reside in the ER in an inactive state.³⁴ Elegant studies by Brown and Goldstein have demonstrated that SREBPs are escorted to the Golgi apparatus by the SREBP cleavage activating protein (SCAP) protein, where they are sequentially processed by site 1 and site 2 proteases to liberate the cytosolic domain that translocates to the nucleus and regulates target gene expression.^{6, 34–36} SCAP-assisted transport to the Golgi and the subsequent proteolytic processing of SREBP-2 is inhibited by sterols in a negative feedback loop.³⁵ SREBP-1c activation is not regulated by sterols. Instead, SREBP-1c is activated at the transcriptional level by insulin produced by pancreatic beta cells upon carbohydrate ingestion.³⁰ Therefore, hepatic SREBP-1c mRNA and protein levels are decreased upon fasting and dramatically increased by refeeding mice with a carbohydrate-rich diet or by direct insulin infusion.^{37, 38} The mechanism of SREBP-1c mRNA induction by insulin is not completely understood, but it appears that the AKT signaling pathway and SREBP-1c itself and LXR play important roles in SREBP-1c mRNA induction.^{32, 39–42} Mice lacking SREBP-1c in all organs, or site 1 protease (S1P) or SCAP specifically in the liver, display significantly decreased plasma TG due to decreased hepatic TG production associated with decreased expression of lipogenic genes such as *Fasn* and *Acc*.^{6, 36, 43–45} In contrast, transgenic mice that over-express SREBP-1c, SREBP-1a, or SREBP-2 accumulate lipids in the liver and display dramatic induction of genes regulating both TG and cholesterol synthesis,^{46–48} indicating the importance of SREBPs in hepatic lipid synthesis.

ChREBP was originally identified as the transcription factor that binds to the carbohydrate response element (ChoRE) motif in the L-type pyruvate kinase (LPK) gene promoter.⁴⁹ Glucose synergizes with insulin, which signals through SREBP-1c to induce glycolytic and lipogenic genes, and ChoRE is the promoter element that mediates the glucose signal.^{50, 51} ChREBP is a large ~100 kD bZIP transcription factor.⁴⁹ *In vitro* inhibition by siRNA or genetic deletion of ChREBP abolished glucose induction and suppressed the expression in the liver of the *Lpk*, acetyl CoA carboxylase (*Acc*), and fatty acid synthase (*Fas*) genes, suggesting that ChREBP indeed plays an important role in hepatic lipid metabolism.^{52–54} Uyeda and colleagues demonstrated that ChREBP is primarily regulated by both a kinase and a phosphatase at the level of nuclear translocation. Hence, the nuclear translocation of ChREBP is inhibited by protein kinase A (PKA)-mediated phosphorylation, while promoted

by the protein phosphatase 2A (PP2A) phosphatase, which is activated by glucose.^{31, 55} XBP1s is induced by glucose, and our data suggest that this occurs post-transcriptionally; hence there appear to be similarities between the signals that regulate XBP1s and ChREBP, a topic we are currently exploring.

XBP1 and Hepatic Lipogenesis

Remarkably, deficiency of XBP1 in the liver (Xbp1Δ) led to profound decreases in serum TG, cholesterol, and free fatty acids without causing hepatic steatosis. XBP1 was induced upon high-carbohydrate diet feeding and directly activated key lipogenic genes in the liver. The evidence for this was 1) diminished serum levels of triglycerides, cholesterol, and free fatty acids in XBP1^{-/-} mice, 2) diminished hepatic triglyceride secretion, 3) diminished free fatty acid and sterol biosynthesis in primary XBP1^{-/-} hepatocytes, 4) transactivation of a subset of genes encoding key lipogenic enzymes by XBP1, and 5) direct binding of XBP1 to endogenous promoters of these lipogenic enzymes. Hence, we have uncovered a surprising and physiologically relevant function of XBP1 in hepatic lipogenesis that is unrelated to its previously established function in the ER stress response.⁹ We conclude that XBP1 is a multitasking transcription factor that is essential for protein secretory function (plasma cells, pancreatic exocrine cells) in some organs but is not required for handling protein loads in other organs, such as adult liver. Instead, in these organs it controls transcriptional regulatory pathways such as lipogenesis.

Our data showed that the low plasma lipid levels observed in Xbp1Δ mice are primarily due to decreased *de novo* synthesis of lipids in the liver, rather than to defective assembly and secretion of VLDL particles, consistent with the normal folding and secretion of apoB-100 that we observed. In both mammals and yeast, XBP1 (Hac1p) is thought to regulate membrane lipid biosynthesis and ER biogenesis.^{56,57} It is intriguing to speculate that mammals have evolved to employ XBP1 for both phospholipid biosynthesis during the development of professional secretory cells and triglyceride synthesis in the liver for long-term energy storage. It is not fully understood how Hac1p and XBP1 regulate phospholipid synthesis, but in yeast it appears that Hac1p antagonizes the transcriptional repressor Opi1p, allowing the activation of genes encoding phospholipid biosynthesis enzymes.⁵⁶ XBP1 increases enzymatic activities in the phospholipid biosynthesis pathway, although its direct transcriptional target or targets are not known.⁵⁷ We do not yet understand precisely how XBP1 controls the synthesis of lipogenic enzymes. What is its binding site in the promoter regions of these genes? Does it act alone or in partnership with other known transcription factors such as SREBP, ChREBP, LXR, Mlx, PGC1α, and PGC1β? The mechanism by which XBP1s induces the transcription of genes encoding lipogenic enzymes is as yet unknown.

The profound increase in XBP1s protein in the liver of mice fed a high-fructose diet suggests that the rheostat that adjusts levels of XBP1s may react to the abundance of ingested carbohydrate. Glucose itself, but not insulin, appeared to be the sensor since XBP1s protein levels did not change in either fasted mouse liver or hepatocytes treated with insulin. In contrast, XBP1s protein was significantly induced in hepatocytes cultured under high-glucose conditions, suggesting that XBP1 is controlled by glucose, most likely at the post-translational level. Glucose has been shown to induce dephosphorylation and subsequent nuclear translocation of ChREBP through activation of PP2A.^{31,55} The phosphorylation of cellular XBP1s may be similarly regulated by glucose. The precise signals that induce the expression of XBP1s protein in the setting of high-carbohydrate feeding are yet to be determined. The mechanisms that lead to the post-transcriptional or post-translational induction of XBP1s protein are unknown. XBP1 is a ubiquitinated, phosphorylated protein

with a short half life. It will be important to understand how the signals identified above regulate levels of XBP1s protein in the liver.

XBP1 and Models of Metabolic Disorders

We and others showed previously that ER stress is present in the liver of genetically manipulated or high-fat diet–induced obese mice, likely from increased free fatty acids or TG.^{58–61} In this setting, ER stress-mediated Jun N-terminal kinase (JNK) activation inhibited insulin signaling, linking obesity with the development of hepatic insulin resistance. Our recent work reveals that XBP1 deficiency does not induce noticeable ER stress in the liver, but does profoundly reduce fatty acid production. It will be important to test whether and how modulation of XBP1 affects the development of 1) the constellation of obesity, insulin resistance, hepatic steatosis, and non-alcoholic steatohepatitis (NASH) and 2) hyperlipidemia and atherosclerosis. Finally, the *Xbp1Δ* liver displays a qualitatively and quantitatively normal lipid profile with no hepatic steatosis in the presence of profoundly decreased LDL cholesterol levels. This is in contrast to microsomal triglyceride transfer protein (Mttp) and apolipoprotein B (ApoB) mutant mice, where lipid accumulates in the liver due to impaired VLDL assembly/secretion,^{62–65} and to mutant mice lacking SREBPs, in which hepatic lipids are diminished.^{36,43–45} Hence small molecules that block XBP1 activity in the liver may be useful therapeutics in patients with dyslipidemias.

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Figure 1.
Schema of XBP1 in hepatic lipogenesis.